ISSN: 0976-4607
Review Article

International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

Time Controlled Chronomodulated Drug Delivery System - A Critical Review

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ABSTRACT

Chronomodulated drug delivery (CDDS) or Pulsatile drug delivery system (PDDS) is the actually time-delayed or time controlled drug delivery system. Chronomodulated drug delivery system controls the lag-time of some factors like enzymatic activity, GI-Motility and pH etc. Chronopharmaceutics denoted as temporal changes in the ADME process. In which systems are fabricated accordingly to the circadian rhythms of the human body. Nowadays drugs are delivered in controlled release like immediate release, extended release and prolong release. Many of the diseases are rheumatoid arthritis, blood pressure and asthma are the occurring at morning time. A chronomodulated drug delivery system was designed according human bio-clock. Pulsincap (chronomodulated drug delivery system) has to be designed that provide a rapid drug release is achieved after lag-time in a way that CDDS deliver the drug at the right time and right place. It will give the relief to patients who suffering with rheumatoid arthritis, hypertension and asthma.

Keywords: Time- delayed, Lag-time, CDDS, Bio-clock.

INTRODUCTION

In the pharmaceutical field many of the drug delivery system technologies are there in advancement. Recent decade more interest in designing of better and optimized drug delivery system, in which some hurdles are overcome in designing of drug delivery systems or new discovery for already existed drug molecule (Davis SS, 1998). Normally drug was administration from the oral route for patient compliance. Oral control drug delivery is shown in the figure no. 1. Here different types of controlled release profiles are there like sustained release, extended release, controlled release and pulse release. Pulse release is comes under immediate release at desired time. These are release profiles shown in the therapeutic index of drug delivery system (Marroni A, 2005).

Nowadays are mainly focus on prevention of drug wastage, right place and right time of the formulated drug of delivery system. Chronomodulated drug delivery system is the most efficient system in delivery the active pharmaceutical ingredient (API) (Youan B, 2004). Here many of drugs are used for designing of chronomodulated drug delivery systems. But all of the drugs are not suitable for this technology, because drugs are subjected to large metabolic reduction and short half-life. For example drugs are having large metabolic reduction, due to first pass metabolism is cause to reduction of bioavailability of drug, and it is cause for greater degradation of drug.

In case in sustained release formulation continuously taking of the drug to body it may lead to adverse drug reaction. For example , diabetes mellitus sustained release formulation of drug contains sulpher and urea derivatives may effect on pancreas, so drugs should not deliver at a constant rate, because drug may lost therapeutic index with continuous taking constant dose level of drug with constant time(Shirisha VNL, 2012).

Chronomodulated drug delivery is the fabrication and assessment of drug molecule accordingly human bio-rhythms (Youan B, 2004). Chronomodulated referred as the pulse of concentration release after the lag-time from drug delivery system in a periodic pattern control is noted pulsatile drug delivery system: certain amount of API was immediate release with in short period after lag-time is shown in figure.2 (Saeger H, 2004).

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The present review explains as the chronomodulated drug delivery technologies in upcoming pulsatile drug technologies.

Advantages of chronomodulated drug delivery system (Shirisha VNL, 2012)

- Decrease the gastric retention time
- Improve bioavailability
- Reduce the adverse effects and improve tolerance
- Prevention of drug wastage
- Deliver the API at right time and right place with required amount

Disadvantages of chronomodulated drug delivery system (Shirisha VNL, 2012)

- Cost of production is high
- Newer equipment should be provide
- Various variables are effect

Requirement of CDDS for Peak symptomatic diseases

Many of the diseases are occurring at morning time. Before going to designing drug delivery system, we have to know about the disease physiology. In the physiology of disease, a pharmaco-kinetics and pharmaco-dynamics profiles are not constant in rhythmic cycle (Conte U, 1989). Hypertension, asthma and rheumatoid arthritis are the disease occurring at early morning time or night time. For example cardiovascular diseases (blood pressure, heart stroke and blood flow) are functioned accordingly cardian rhythms (Pollock DC, 2001).

Excipients used in the CDDS

Designing of drug delivery systems polymers are play key role in delivery of drug. PLGA (Poly-Lactic-Glycolic-Acid), Hydroxy propyl methyl cellulose (HPMC), Natural polymers (Hupu gum, guar gum, xanthan gum, gum karaya and Gellan gum) are using polymers (Michael PL, 2009). And here hydro-gel plugs are made with matrix type polymers, matrix polymers will have more swelling index and fast disintegration or super disintegration property. PLGA has more degradation property. For film coating of capsules some Excipients are using like Cellulose acetate phthalate (CAP), Eudrazit LS100 and Ethyl cellulose (Shirisha VNL, 2012). These polymers are bio-degradable polymers, bio degradable polymers are with standing increasing the solubility of drug and rapid release of drug. Hydrogel polymers are also water soluble materials, which was gives a matrix forming when contact with aqueous phase and release drug immediately (Ura J, 1992).

Pulsatile Drug Delivery System

Pulsatile drug delivery system is time and site-specific drug delivery system, thus gives special and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid release of certain amount of drug molecules within a short time period immediately after a programmed lag-time period (Fangri O *et al*, 2011).

Classification of Pulsatile Drug Delivery Systems

Pulsatile systems can be classified into single- and multiple-unit systems pulsatile systems are basically time controlled drug delivery systems in which the system controls the lag-time factors like pH, enzyme activity, gastro-intestinal motility etc (Survase S *et al*, 2007).

Time controlled systems can be classified as (Gothoskar AV et al, 2005)

1. Time controlled pulse delivery
2. Stimuli induced pulse delivery
3. Externally regulated pulse delivery

Time Controlled Pulsatile Systems

The principle of time controlled drug delivery systems is that the release of the drug according to a predetermined time after a lag period (delayed release systems) to achieve maximum therapeutic index and minimal toxic effect (Survase S *et al*, 2007).

These are sub-classified as single-unit, multiple-unit systems. Single-unit systems are designed by coating the system either with soluble enteric coating (Shirisha VNL, 2012).

1. Single-unit systems
a) Capsule systems
b) Capsule with osmosis
c) Capsule with erodible/soluble polymer
d) Capsule with rupturable carrier
2. Multiple-unit systems
a) Rupturable coating system
b) Osmosis basis pulsatile system
c) Erodible polymer coating

Time controlled single-unit capsule based systems

Single-unit systems are mostly developed in capsule. The lag-time is controlled by a plug, which was swelling, and the drug is released as a "Pulse" from the insoluble capsule body (Linkwitz A, 1994). Different single-unit capsular pulsatile drug delivery systems have been developed. A general structure of such systems consists of an insoluble capsule body contains a drug and a plug. The plug is dissolved after a lag time owing to swelling or dissolution. Different types of capsule base systems are,

1. Pulsincap® System

The Pulsincap® system shown in figuer.3 (Scherer Drug Delivery System) is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. A highly swellable, alternatively, plug made of hydrophilic (water soluble) polymers was used to cover the drug contents into the capsule body. When this capsule comes in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes away itself outside from the capsule and releases the drug immediately. Various types of polymers used for designing of the hydro gel plug are hydroxyl propyl methyl cellulose (HPMC), polyvinyl alcohol

(PVA), poly methyl methacrylates, polyvinyl acetate and polyethylene oxide (Sarasija S *et al*, 2005). The length of the plug was used as controlled the lag time. When capsule made an enteric coating, the system was evaluated for time-dependent delivery as well.

Various Technologies of Pulsincap Drug Delivery

Many technologies have been developed to deliver the drugs to the body according to the biological rhythm of the disease. The technologies developed to achieve this aim, which has been approved by US-FDA for Chronotherapy of the diseases.

1. Diffucaps® Technology

Developed by Eurand Pharmaceuticals Ltd. Diffucaps is a multi-unit system comprised of multiple layers of drug, excipients, and polymer membrane to control the drug release rate. Diffucaps time, pulse beads are <1.0 mm in diameter and can be filled into capsules. The beads contain a layer of water soluble polymer to control the solubility of a drug by creating an optimal pH environment for drugs that exhibit poor solubility in physiological fluids. The beads can contain a solid-solution of drug and prevent the crystallization to enhance bioavailability by maintaining the drug in its amorphous form (Amidone GL, 1993). What are the advantages of Diffucaps ® were discussed below

a) Drugs exhibiting poor solubility in lower intestinal pH and in physiological fluids.

b) It will give multiple release profiles in the same dosage form.

2. CONTIN ® Technology

Purdue Pharma was formulated COTIN® Technology. This technology provides for closer control over the amount of drug released to the blood plasma, and benefits patients in terms of reducing the number of doses they no need to take every day, providing more effective control of their disease and reducing side effect. Molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and react the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This composition of the complex having a matrix in controlled release formulations since it has a semi permeable membrane, it may be varied. This technology has leads to the development of tablet forms for respiratory drugs, opiod analgesics and other drugs (Survase S *et al*, 2007).

3. CODAS® (Chronotherapeutics oral drug absorption system)

Elan Corporation, USA, developed CODAS® technology. Delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded time, pulse release (TPR) beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As fluid from the GI tract comes into contact with the polymer-coated beads, the water soluble polymer slowly dissolved, and the drug diffuses from the resulting pores in the coating (Janugade BU, 2009). The water insoluble polymer continues to act as a barrier coating, maintaining the controlled release of the drug.

4. PORT® technology

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug (Saeger et al, 2004). It contains a polymeric core coated with a semi-permeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semi-permeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need (Sachin S, 2007).

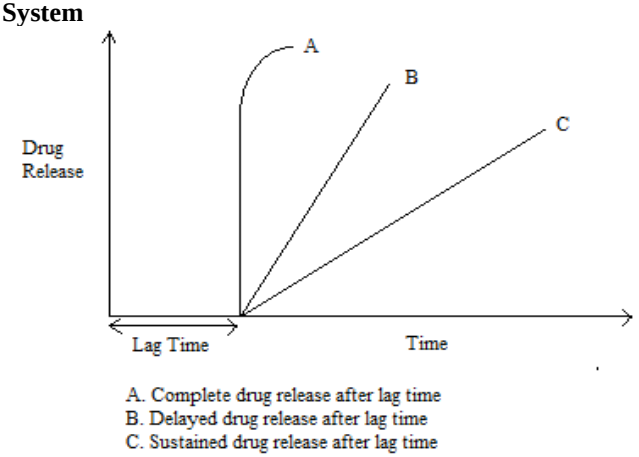
Table.1 Diseases require a chronomodulated drug delivery system (Ueda S, 1994)

Chronological Disease Behavior	Diseases	Drugs Used
Acid secretion is high in the Afternoon and at night	Ulcer	H2 blockers
Precipitation of attacks during night or at early morning	Asthma	β2 agonist, Antihistamines
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Heart attack, Blood pressure	Nitro-glycerine, calcium channel blocker, ACE inhibitors
Pain in the morning and more pain at night	Rheumatoid Arthritis	NSAIDs, Glucocorticoids
Increase in the blood sugar level after meal	Diabetes	Sulfonylurea, Insulin
Cholesterol synthesis is generally higher during night than day time	Hypercholesterolemia	HMG Co-A reductase inhibitors

Table.2 Marketed Formulations of Pulsincap Technology

Technology	Mechanism	Proprietary Name and dosage form	API	Disease
Oros®	Osmotic mechanism	Covera-H5*; XL tablet	Verapamil HCL	Hypertension
Codas®	drug diffuses from the resulting pores in the coating	Codas®	Diclofenac sodium	Inflammation
Diffucaps®	Multiparticulate system	Innopran*; XL tablets	Verapamil HCL, Propranolol HCL	Hypertension
Pulsincap®	Rupturable system	PulsincapTM	Dofetilide	Hypertension

Figure.1 Drug release Profile of Pulsatile Drug Delivery System



A. Complete drug release after lag time
B. Delayed drug release after lag time
C. Sustained drug release after lag time

Figure.2 Drug release pattern after lag-time

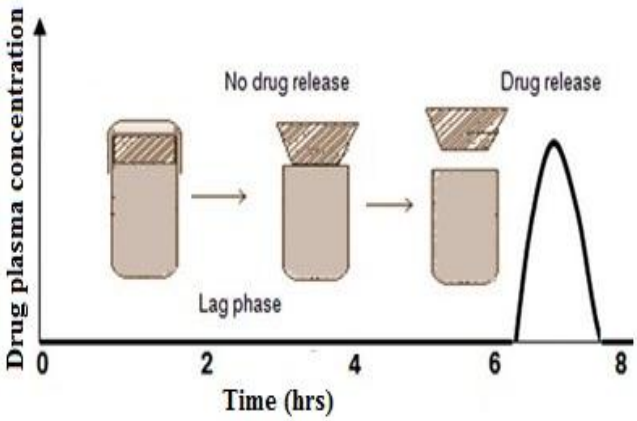
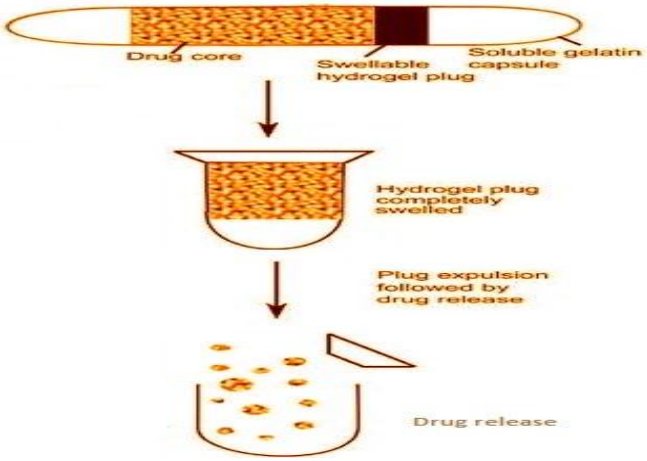
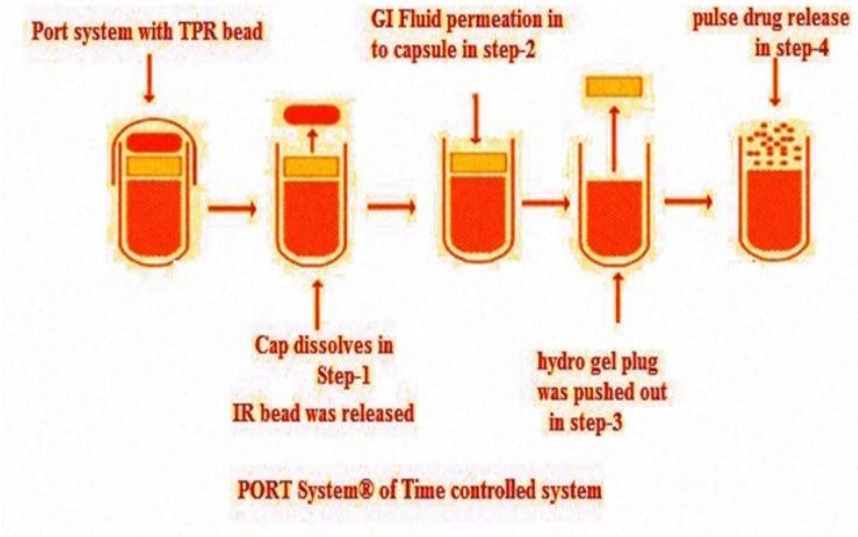


Figure.3 Drug release profile of The Pulsincap® system



Figurre.4 Diffucaps® Technology

Figure. 5 PORT® technology of controlled release system



CONCLUSION

A chronomodulated drug delivery system that can effectively treat diseases. . Products that are currently under development for commercialization are for the delivery of enzymes, proteins, hormones, analgesics and other pharmaceutical compounds. a new approach to the development of novel drug delivery system-CDDS (Chronomodulated Drug Delivery System). As timing of drug administration in disease therapy has significant impact upon treatment success, CDDS in future is certainly going to gain popularity. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. Different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent days.

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